

APCs and MHCs

Introduction

In #4: *Innate Immune Response*, we learned that the local phagocytes activate local inflammation, calling more phagocytes in to help. Blood (and therefore leukocytes) is brought to the site of inflammation via arteries. Fluid, including leukocytes, is drained by the veins and lymphatics. In this lesson, we talk about the process by which the innate and adaptive immune systems are bridged, how a local or circulating leukocyte leaves the site of inflammation, and brings pathogens back to secondary lymphoid tissue, the forward command post. This leukocyte isn't running from the fight—it's bringing valuable intelligence about what they're fighting. The command post is where T cells and B cells analyze the data, and produce highly specialized fighters to win the war. This lesson is about **presentation of antigen**. While most texts use Roman numerals for their MHC molecules (MHC-I and MHC-II), we've used Arabic numerals instead (MHC-1 and MHC-2), for avoidance of ambiguity. When an MHC molecule exists on its own, unbound to an antigen, it's referred to as MHC-1 or MHC-2. When it's combined with an antigen, it's referred to as MHC-1-Ag or MHC-2-Ag, (Ag standing for antigen).

APCs and MHCs

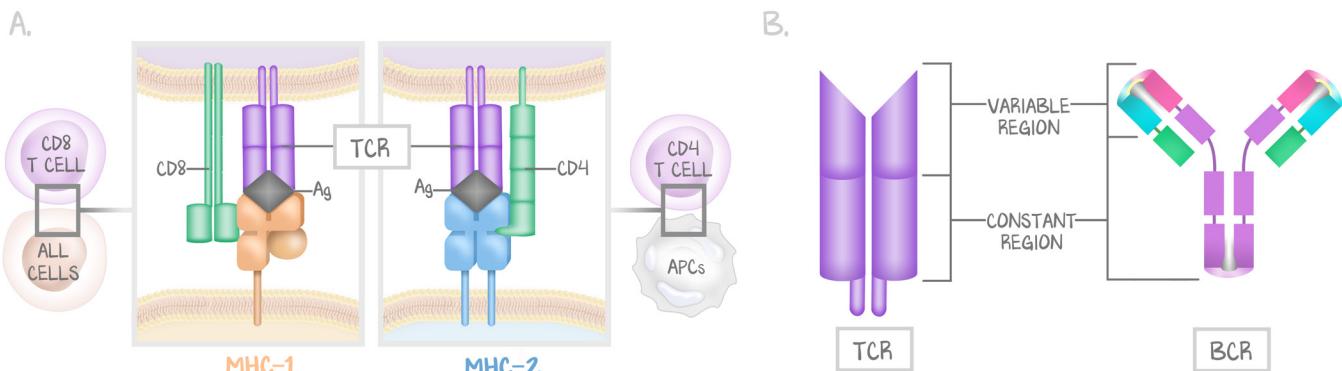
Antigen-presenting cells (APCs) use **major histocompatibility complex** (MHC) proteins to display foreign antigen. The APC has the antigen inside itself. The APC has the MHC inside itself. The APC then puts both the antigen and the MHC together and displays the antigen-MHC combination to naive T cells. What the T cells see will determine what happens next. The antigen can be either from the cell's own nucleus (**all cells** can do this MHC-1-Ag presentation), or from the phagocytosed antigen (**only professional APCs** can ingest, digest, and present this MHC-2-Ag). Professional APCs are cells such as macrophages—the phagocytes.

MHC-2 has four domains and uses CD4 costimulation. MHC-1 has 3 domains and a $\beta 2$ microglobulin, and is stabilized by CD8. This is super crucial to commit to memory. MHC-2 and CD4. MHC-1 and CD8. Always and forever.

MHC-2s are read by **CD4 T-helper cells**. T-helper cells can then do multiple things down multiple pathways. More on that in #10: *T-Cell Activation*. A helpful reminder is to take eight (8) and divide it by the MHC number. Or go the other way, use multiplication; $2 \times 4 = 8$ and $1 \times 8 = 8$. So the product either way should be 8.

8/MHC-1 is 8/1, which is 8. CD8 T cells read MHC-1 molecules.

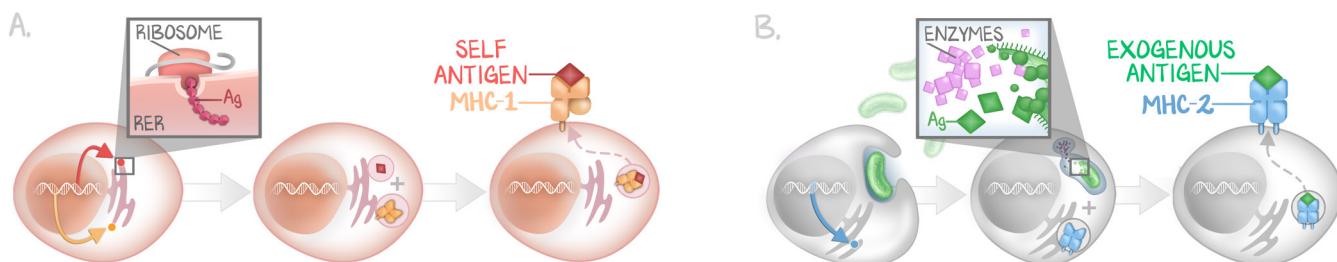
8/MHC-2 is 8/2, which is 4. CD4 T cells read MHC-2 molecules.

**Figure 5.1: Structure of MHC-1 and MHC-2**

MHC-1 has 4 domains, but one of them is $\beta 2$ microglobulin, whereas MHC-2 is an intact four-leaf clover. The reason this is important is so that we visually differentiate MHCs from immunoglobulins and T-cell receptors. The actual structures of MHCs and immunoglobulins are fairly similar, with variable domains, constant domains, and a cytoplasmic transmembrane region. Although the structures can appear very similar, each has an important and different role in signaling and cell activation.

MHC-1s Are for All Self-Cells

MHC-1 molecules are expressed on **all nucleated cells**. It's a way for all self-cells to be screened for safety. If the cell is doing well, it simply says the safe-word to the T cell via MHC-1, and the T cell leaves it alone. The cell does not have to communicate its distress. There is no "help me" signal, no inflammatory cytokine is needed. Simply failing to provide the safe-word is enough for the T cell to act (if the cell is in trouble it can't communicate that it is okay, so that lack of communication is the signal to the T cell that the cell needs help). The naive T cell activates (see lesson #10: *T-Cell Activation*). **CD8 cytotoxic T cells** make cytokines that kill the broken cell (apoptosis). Both the MHC-1 and the antigen being presented are made **by the host cell's own nucleus** (they're technically paired in the endoplasmic reticulum via TAP complexes, but the host cell is making both antigen and MHC-1). And because it's getting the antigen from itself, it's considered the **endogenous antigen**. The host cell "speaks the safe-word" with a protein. And since it makes the protein, the only way a host cell wouldn't say the safe-word correctly is if the nucleus (and subsequently the DNA) were compromised. DNA compromise in a cell is usually caused by a **virus** or by **malignant transformation**—problems with cells that can corrupt the genetic code and cause the "wrong" protein to be made. Bacteria don't do that to cells—only viruses and cancers mess up the cells' own DNA. And that's what the T cells are looking for on MHC-1-Ag presentation.

**Figure 5.2: Presentation of Antigens by APCs**

(a) All nucleated cells produce both an endogenous antigen from their own DNA and the MHC-1 protein from their own DNA. They're both packaged in a vesicle in the RER, where they're sent via the Golgi apparatus to the cell surface. There's no CLIP protein in MHC-1 presentation. (b) Professional antigen-presenting cells use phagocytosis to ingest a foreign pathogen, use lysosomes to digest the pathogen, then combine MHC-2 proteins made by their own nucleus with fragments of the digested pathogen (discrete antigens) and present the MHC-2-Ag to the cell surface.

MHC-2 is for APCs Only

Unlike MHC-1, which all cells express, **MHC-2** molecules are expressed only on **professional antigen-presenting cells** (APCs). And although APCs also have the MHC-1 pathway (they, too, need a safe-word to make sure they're working properly), professional APCs possess the **extra ability** of presenting **exogenous antigens** that they find through phagocytosis. The process of identifying and displaying a foreign antigen necessitates the exogenous antigen to be phagocytosed and degraded in a lysosome. MHC-2 molecules are also added to lysosomes where foreign material is being degraded by lysozymes, allowing the possibility for the MHC-2 molecule to bind to an antigen. But it isn't as simple as just, "add some MHC-2 to a lysosome." It's a little more complicated than that.

The MHC-2 pathway requires the use of a class 2 invariant chain peptide called **CLIP**. The CLIP stabilizes the MHC-2 molecule so it's not degraded in the lysosome. It also prevents any binding of any peptide to the MHC-2 until the CLIP is removed. **HLA-DM** (another protein; just memorize its name) is found in the late endosome, long after bacteriolysis has occurred. HLA-DM displaces CLIP, opening up an antigen-binding site, allowing the MHC-2 molecule, now free of CLIP, to bind whatever pieces of destroyed bacteria it can find. These pieces of destroyed bacteria are antigens. If there's a protein that MHC-2 can bind to, it binds it, and that binding of antigen to MHC-2 sends the signal for the MHC-2-Ag complex to be sent to the cell surface. If no antigens bind the MHC-2, even in the absence of the CLIP, then it doesn't have anything to show, and the MHC-2 molecule never gets sent to the surface.

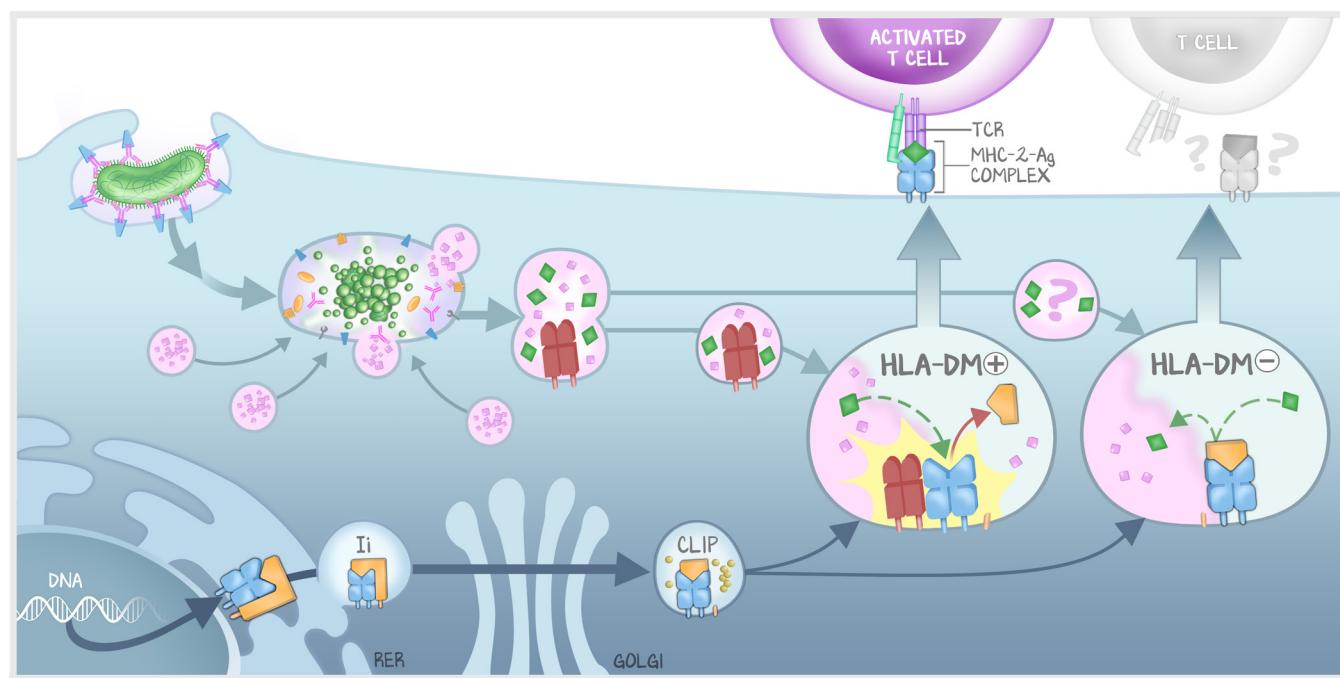


Figure 5.3: CLIP and DM Mechanism

MHC-2 molecules are made with the primordial invariant chain (Ii) protein attached to the antigen-reading site. Processing through the Golgi results in the CLIP being clipped, but still attached to the antigen-binding region. When in a lysosome with a DM+ protein, the CLIP is removed and the antigen allowed to bind. Only the MHC-2-Ag complex can activate the T-cell receptor. If there is no DM (DM-), no CLIP is removed, and if the MHC-2 molecule were present on the cell surface, it would not react with the T-cell receptor.

Bridging Innate and Adaptive Immunity: A Review So Far

This is one-third through the Immunology course. See if this makes sense so far. If it does, fantastic. If it doesn't, go back and see if you can find the hole in your knowledge. From here out it's all adaptive immune responses. So make sure you have a good handle on the stuff up to this point, because the adaptive immune response depends on the innate immune system. Understanding how the innate immune system works will help you better understand how the innate and adaptive immune systems interact.

Primary lymphoid organs are where B cells and T cells are made and mature. Secondary lymphoid organs are where they are activated. You don't know anything about activation yet, but we will get there soon.

Let's summarize what we know so far. When a pathogen penetrates the physical and physiologic barriers of the innate immune system, local leukocytes in the tissue encounter the pathogen. The initial response is phagocytosis. This phagocytosis induces the phagocytes to secrete inflammatory cytokines. This inflammation causes vascular events that increase blood flow to the affected area, slow the blood down (stasis), and induce vasodilation to improve vascular permeability. This allows circulating leukocytes to be delivered to the site of inflammation AND slow down enough to get to the edge of the capillary. That same inflammatory signal from the local leukocytes induces integrin expression on circulating leukocytes, which allows them to stop at the site of inflammation, then exit the capillary. Leukocytes are drawn to the source of antigen by chemotaxis. At the same time, a very small percentage of these same phagocytic cells, now both the circulating ones and the local ones, leave the fight to bring antigens to the secondary lymphoid organs. These phagocytic cells are special cells called antigen-presenting cells. Antigen-presenting cells have MHC-2, which allows them to bind to digested pathogen, presenting a small portion of the pathogen (that small portion being the antigen) to T cells. MHC-2 presents antigens from invaders that have been phagocytosed and destroyed. MHC-2-Ag complexes on the surface of APCs are identified by CD4 T-helper cells, which are activated. We don't know what "activated" means yet (this is repeated from the previous paragraph on purpose).

AND, regardless of the state of inflammation, ALL human cells produce MHC-1. MHC-1 presents the self-antigen, made by the host cell nucleus. If there's something wrong with that MHC-1-Ag, it means that something's wrong with the host cell. Either it's infected or it's turned malignant. In either case, CD8 cytotoxic T cells read the signal and do something in response (you don't know what that something is yet).